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CASE-CONTROL STUDIES OF ACUTE MYELOID LEUKEMIA (AML) AND NON-HODGKIN'S LYMPHOMA (NHL) IN SHANGHAI

Prepared jointly by

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June 12, 2000

INTRODUCTION

In 1979-1981 the Institute of Occupational Medicine, Chinese Academy of Preventive Medicine (CAPM), carried out a national survey in China, in which more than 500,000 workers were identified to have been exposed to benzene (Yin et al., 1987a). The 95% range of benzene concentrations at workplaces was 0.06-844.74 mg/m^3 (0.02-266 ppm). Subsequently, 28,460 of these exposed workers from a variety of industries in 12 cities and 28,257 unexposed workers from the same cities were included in a historical cohort study (the "CAPM" study). The results were reported in a number of publications (Yin and Li, 1986; Yin et al., 1987b; Yin et al., 1989). A total of 25 leukemia deaths and 5 incidence cases were reported among the exposed workers, while 4 deaths among the unexposed workers were attributed to leukemia. The standardized mortality ratio (SIR) of leukemia for the exposed workers in comparison to the unexposed workers was 5.74 ($p < 0.01$). No exposure-response analysis was performed, but the authors reported actual benzene measurements from locations where leukemia deaths and cases were observed (Yin and Li, 1986; Yin et al., 1987b; Yin et al., 1989). Exposure levels reported were as high as 5,508 mg/m^3 or 1,732 ppm. In 1988, Li and Yin published a case-control study of leukemia and benzene exposure in four cities in China (Li et al., 1988). The reported relative risk was 3.4. No benzene exposure levels were available in the case-control study.

Since 1987, the US National Cancer Institute (NCI) has collaborated with CAPM in expanding and updating the Chinese benzene study. The previous study was expanded to include 74,828 benzene-exposed workers and 35,805 unexposed workers who were employed for any length of time between 1972 and 1987 at 712 factories in 12 cities (the "CAPM-NCI" study). The general methods and resources of the expanded study were described by Yin et al. (1994). In a second paper, an historical benzene exposure assessment to characterize benzene exposure profiles of the cohort members was outlined (Dosemeci et al., 1994).

Based on comparisons between the exposed and unexposed workers, increased mortality risk ratios (RR) were reported for a variety of cancers (Yin et al., 1996). Some exposure-response analyses in terms of cumulative exposure (ppm-years) for selected disease categories were reported by Hayes et al. (1996). In another paper, Hayes et al. (1997) reported dose-related incidence of hematologic neoplasms. For leukemia, the RR was 2.5 (95% CI: 1.2-5.1). For acute non-lymphocytic leukemia (ANLL), the RR was 3.0 (95% CI: 1.0-8.9). The RR for non-Hodgkin's lymphoma (NHL) was 3.0 (95% CI: 0.9-10.5). The trend between ANLL and cumulative exposure was close to, but did not achieve, statistical significance ($p = 0.06$). For NHL, the highest risk (RR = 7.8) was observed among "chemical" workers, which included "organic, insecticide, and benzene production workers."

Although the Chinese benzene study was one of the largest studies in terms of number of exposed workers, some results were based on comparisons to small numbers of cases for disease categories of interest in the unexposed group. For example, there were only 4 ANLL cases and 3 NHL cases among the unexposed workers. In the Chinese benzene study, results depended not only on the number of deaths in the exposed group but also on the number of deaths in the unexposed group. The small number of deaths in the unexposed group rendered the results unreliable.

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The exposed workers were employed in a variety of industries. In the CAPM study, 64% of the exposed workers were either painters or paint production workers (Yin et al., 1987b). In terms of exposures, only 5% were exposed to benzene only (Yin et al., 1987a). The potential problem of concomitant exposures complicated the interpretation of the results in relation to benzene exposure (for example, the NHL increase in workers exposed to both benzene and insecticides).

When compared to the unexposed workers, the exposed workers were reported to have increased risks in a variety of diseases. More specifically, increased mortality risks among exposed male workers when compared to unexposed male workers were reported for many specific cancer sites which have not been demonstrated to be related to benzene exposure in other studies; including lung cancer, liver cancer, stomach cancer, intestinal cancer, esophageal cancer, and nasopharyngeal cancer. For example, no study has ever demonstrated an association between benzene exposure and nasopharyngeal cancer. These observations raised potential concerns regarding the comparability of the unexposed workers, potential under-ascertainment of cancer among the unexposed workers, and confounding exposures (or other risk factors) in the exposed group (Yin et al., 1989).

One of the areas of uncertainty in the Chinese benzene study involved the exposure estimates. Comparing the assumptions used in the development of estimates and the exposure estimates themselves to actual data reported identified a number of inconsistencies and/or inadequacy of exposure categories. For example, the actual average exposure of spray painters (full-day exposure) at a factory in Shanghai in 1965-1969 was 331 mg/m^3 (104 ppm), whereas the estimate developed by Dosemeci et al. (1994) for spray painters in the same time period was 22.1 ppm. There are other similar examples. It appeared that the exposure estimates were consistently lower than the actual exposure data. Dosemeci et al. (1994) recognized that little confidence could be attached to the estimates: only 2% of the estimates for the time interval 1949-1959 and only 6% of the estimates prior to 1975 were rated in the "high confidence" category by Dosemeci et al. Exposure-response analyses based on these exposure estimates should be interpreted with extreme caution. A detailed critique of the exposure assessment developed by Dosemeci et al. has been published by Wong (1999).

Both CAPM and NCI have made substantial efforts in studying the relation between benzene exposure and malignancies. Unfortunately, because of the problems discussed above, the results of the CAPM-NCI study are difficult to interpret. Nevertheless, because of the large number of Chinese workers who are or have been exposed to relatively high levels of benzene (compared to, for example, levels at refineries in the US), China represents a unique opportunity for investigating the carcinogenic effects of benzene.

In this proposal, we will outline an epidemiologic investigation to assess the relation between exposure to benzene and the risk of developing acute myeloid leukemia (AML) or non-Hodgkin's lymphoma (NHL) in China. More specifically, the investigation will consist of hospital-based case-control studies of male and female patients diagnosed with AML or NHL in Shanghai.

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PROPOSAL

Objectives

The objectives of the proposed hospital-based case-control studies of AML and NHL in Shanghai are as follows:

1. To determine the risk of developing AML or NHL (and major subtypes) among workers exposed to benzene in Shanghai.

2. To quantify the exposure-response relations between exposure to benzene and AML or NHL among these workers.

3. To determine other risk factors (e.g., occupational exposures other than benzene) of AML or NHL among these workers.

Reasons for choosing Shanghai

Shanghai is the largest city in China, with a population of 13 to 14 million. A wide variety of industries are located within the metropolitan area, and benzene is and has been used in many industries in Shanghai. The reasons for choosing Shanghai as the location for our investigation are summarized below.

1. The largest data contributor in the CAPM-NCI cohort study.

2. One of the sites of the CAPM case-control study.

3. Site of the CAPM-NCI clinical investigation.

4. Large population (13-14 million).

5. Major medical establishments (universities, hospitals, tumor registry).

6. Experienced local investigators.

7. A wide variety of industries in the area.

8. A wide range of benzene exposure levels.

9. Documented employment histories from employers through the Shanghai Center for Disease Control (CDC).

10. Availability of historical measurements of benzene exposure at workplaces.

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Identification of AML/NHL cases and matched controls

All cancer cases diagnosed in Shanghai are reported to the Shanghai Tumor Registry. Thus, the Shanghai Tumor Registry will be our primary data source for AML and NHL cases. Other sources will consist of Shanghai Medical University affiliated hospitals (including the Hua Shan Hospital), other major hospitals in Shanghai, and members of the Shanghai Hematology Association. The final selection of participating hospitals or other health care facilities will be determined by the Shanghai Medical University.

Both male and female patients will be eligible. The diagnoses of all identified cases of AML and NHL will be verified. In addition, subtypes of AML and NHL will also be made.

Controls will be selected from other patients at the same hospitals or health care facilities. Patients with other lymphohematopoietic cancers or blood disorders will be excluded from selection. Matching variables will include gender, age and year of diagnosis.

It is estimated that the study will consist of 500 AML patients, 500 NHL patients and 1,500 controls. The study subjects will be enrolled on a prospective basis, and it is estimated that it will take 3 to 4 years to reach the required study size.

Information on risk factors

Demographic data, lifestyle information, medical histories and employment histories will be obtained from medical records and through the use of a questionnaire. A questionnaire (in Chinese) has been tested in a sample of AML and other patients at the Shanghai Medical University Hospital during a feasibility trip to Shanghai in 1998 by Otto Wong and Fu Hua. It is anticipated that only a few minor modifications will be necessary in finalizing the questionnaire.

For study subjects identified to have worked at factories with potential benzene use, copies of employment records will be obtained from the employers through Shanghai CDC. Measurements of exposures to benzene and other chemicals at these factories and other relevant documents (such as raw materials used, work practice and engineering controls) will be obtained from the employers as well as from Shanghai CDC.

Exposure estimates specific to job title, department, factory and calendar year will be developed. Based on employment histories and exposure estimates, an individualized exposure profile will be developed for each exposed study subject. These individual exposure profiles will be used in the epidemiologic analyses.

Epidemiologic analyses

Both stratified analyses (the Mantel-Haenszel χ^2 procedure) and multivariate analyses (logistic regression) will be used in assessing the relation between exposure to benzene and the risk of developing AML or NHL. Exposure variables will include type of industry, type of

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occupation, length of exposure, calendar year, cumulative exposure, truncated exposure, and peak exposure. These analyses will determine whether there is an increased risk of AML or NHL among workers exposed to benzene in Shanghai. If there is an increased risk, the exposure-response analysis will determine the level of exposure associated with the increased risk.

Similar analyses will be conducted to assess the relations between other concomitant exposures and the risk of developing AML or NHL. Lifestyle factors will also be investigated. Confounding factors will be controlled for in the analyses on benzene exposure.

Data access and collaboration

Cooperation and data access have been obtained from:

- Shanghai Medical University (and all affiliated hospitals)
- Shanghai Tumor Registry
- Shanghai Hematology Association
- Shanghai Municipal Center for Disease Control and Prevention (CDC)

A joint research agreement between Shanghai Medical University and Applied Health Sciences has been signed, and a copy has been filed with the Office of International Exchange Programs at the Shanghai Medical University.

Research team

The Principal Investigators of the case-control studies of AML and NHL will be Professors Otto Wong and Fu Hua. Professor Wong has 28 years of experience in occupational research and has conducted more than 200 epidemiologic studies investigating occupational and environmental cancers. Professor Fu is the Deputy Dean of the School of Public Health, Shanghai Medical University, and has full access to a variety of health data in Shanghai.

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Estimated schedule

It is estimated that the proposed case-control studies of AML and NHL will take approximately 5 years to complete.